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Disappearance of Giant Negative T Waves in Patients With the Japanese Form of Apical Hypertrophy

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Objectives. **The present study investigated the long-term changes in the electrocardiographic (ECG) hallmarks of the Japanese form of apical hypertrophy.**

Background. **Giant negative T waves and tall R waves in the left precordial leads are the ECG hallmarks of the Japanese form of apical hypertrophy. However, the long-term course is largely unknown.**

Methods. **Twenty-nine patients with apical hypertrophy (26 men, 3 women, mean age ± SD 50.4 ± 8.2 years) who showed left precordial giant negative T waves (≤ −10 mm) and tall R waves (≥26 mm) and spade configuration in the left ventriculogram were followed up for 10.9 ± 3.7 years.**

Results. **The intermediate follow-up ECGs (5 to 9 years) showed disappearance of giant negative T waves in 31% and of tall R waves in lead V_5 in 6%. At the long-term follow-up study (≥10 years), loss of giant negative T waves increased to 71%, with average T wave negativity in lead V_4 or V_5 decreasing from −16.5 ± 5.1 to −6.9 ± 4.2 mm. These T wave changes were associated with decreases in R wave amplitude in lead V_5 from 40.7 ± 9.6 to 26.1 ± 13.8 mm, with loss of tall R waves in lead V_5 in 38% of patients and development of abnormal Q waves in two patients.**

Conclusions. **During the long-term follow-up of the Japanese form of apical hypertrophy, giant negative T waves disappeared in association with decreases in R wave amplitude in lead V_5, indicating that these ECG hallmarks are clinical features that evolve progressively during the natural course of the disease.**

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Apical hypertrophy was first described in Japan by Sakamoto et al. (1) and Yamaguchi et al. (2) as a morphologic variety of hypertrophic cardiomyopathy in which hypertrophy is present primarily in the apical region of the left ventricle. This Japanese variety of apical hypertrophy has received considerable attention (3–5) as a condition with the characteristic hallmarks of giant T wave inversion and angiographic spade-shaped appearance of the left ventricle. In subsequent studies (6–12) from centers outside Japan, most of the non-Japanese patients with the apical form of hypertrophic cardiomyopathy did not show the characteristic giant negative T waves. The reason for the different phenotypic expression of apical hypertrophy in different parts of the world is unknown, but it is most likely related to differences in patient selection (13). We (14) previously reported that, when the diagnosis was based on angiographic demonstration of spade-shaped left ventricular configuration rather than echocardiographic assessment, apical hypertrophy could be differentiated into two forms: the Japanese and western forms (14). We, then, proposed that although the western form of apical hypertrophic cardiomyopathy is part of the broad spectrum of hypertrophic cardiomyopathy, as indicated by Maron et al. (6,13,15) and Louie and Maron (10), the Japanese form of apical hypertrophy might constitute a separate disease entity. Nevertheless, controversies persist regarding the precise nature of this entity with respect to the overall disease spectrum of hypertrophic cardiomyopathy (13).

With the increasing number of follow-up years of patients with hypertrophic cardiomyopathy, it has become evident that this condition undergoes striking clinical and morphologic evolution, in some cases eventually progressing to severe left ventricular dysfunction resembling dilated cardiomyopathy (15–20). A long-term follow-up study to assess changes in clinical manifestations of patients with apical hypertrophy could provide important clues to determine the disease entity of this condition. The present report describes dramatic changes in the electrocardiographic (ECG) hallmarks of left precordial giant negative T waves and tall R waves developing in patients with the Japanese form of apical hypertrophy.

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Methods

Study patients. The study group included 29 patients with the Japanese form of apical hypertrophy. All patients underwent left heart catheterization, left ventriculography and coronary angiography. Inclusion criteria were based on angiographic demonstration of spade-shaped deformity of the left ventricle (ratio of apical thickness to middle anterior free wall thickness >1.3), associated with giant negative T waves (≤−10 mm) in lead V_4 or V_5 and tall R waves (≥26 mm) in lead V_5. We excluded patients with asymmetric septal hypertrophy showing a ratio of basal septal to posterior wall thickness ≥1.3 in the parasternal echocardiograms or those having significant coronary artery disease.

Of 49 patients who were admitted to the Kurume University Hospital and met the inclusion criteria between 1970 to 1989, 29 patients had follow-up ECG and echocardiographic examinations at 10.9 ± 3.7 years after the initial diagnosis. There were 26 men and 3 women with a mean age at initial diagnosis of 50.4 ± 8.2 years. Informed consent was obtained from each patient. In the remaining 20 patients who did not have follow-up examinations, mail questionnaire reported one cancer death but no cardiac death.

Electrocardiograms. In the standard 12-lead ECGs, R wave amplitude was measured in lead V_5 and T wave amplitude was measured in the lead of maximal negativity (lead V_4 or V_5) at the initial examination.

Echocardiograms. M-mode and two-dimensional echocardiographic studies were performed with the use of standard criteria (21). A short-axis view of the left ventricle at the level of the mitral valve leaflet tips was obtained and the M-mode echocardiogram was recorded with the M-mode cursor positioned centrally in the two-dimensional image. Septal and posterior wall thicknesses were measured at diastole just before atrial contraction. Left ventricular end-diastolic diameter was determined at the peak of the R wave; end-systolic diameter was taken as the smallest diameter during systole. Left atrial diameter was measured at end-systole.

Statistics. Results are expressed as mean value ± SD. Changes in ECG and echocardiographic variables between the initial and follow-up examinations were compared by two-tailed Student paired *t* test. Univariate linear regression analysis was used to assess the relation between serial changes in T wave negativity and serial changes in R wave amplitude during the follow-up period. A p value < 0.05 was regarded as significant.

Results

Patient characteristics (Table 1). The study group consisted of 29 patients (26 men and 3 women) with the Japanese form of apical hypertrophy. The mean age ± SD at initial evaluation was 50.4 ± 8.2 years (range 30 to 60). Thirteen patients had a prior history of mild hypertension; no patient had a family history of hypertrophic cardiomyopathy. Ten patients were asymptomatic and were referred with precordial T wave negativity alone. Among the remaining 19 patients, chest pain was reported in 6, exertional shortness of breath in 6, palpitation in 5 and dizziness in 2. One patient showed atrial fibrillation; the other 28 had sinus rhythm.

Table 1. Clinical Characteristics of 29 Patients With the Japanese Form of Apical Hypertrophy

Men	26
Women	3
Age (yr)	50.4 ± 8.2
History of hypertension	13
Symptoms	
ECG abnormality only	10
Chest discomfort	6
Shortness of breath	6
Palpitation	5
Dizziness	2
NYHA functional class	
I	13
II	16
III or IV	0
R wave in lead V_5 (mm)	42.0 ± 10.7
T wave in lead V_4 or V_5 (mm)	−16.0 ± 4.6
Ventricular septal thickness (mm)	14.2 ± 3.2
Posterior wall thickness (mm)	14.0 ± 2.8
Left ventricular diameter (mm)	
Diastole	45.8 ± 5.0
Systole	27.8 ± 4.8
Fractional shortening (%)	39.5 ± 7.5
Left ventricular pressure (mm Hg)	
Systole	134.1 ± 23.2
End-diastole	13.9 ± 4.7

Data are presented as number of patients or mean value ± SD. ECG = electrocardiogram; NYHA = New York Heart Association.

By selection, all patients presented tall R waves in lead V_5 (mean height 42.0 ± 10.7 mm) and giant negative T waves in lead V_4 or V_5 (−16.0 ± 4.6 mm). The two-dimensional and M-mode echocardiograms showed mild to moderate thickening of the interventricular septum (mean thickness 14.2 ± 3.2 mm) and the left ventricular posterior wall (14.0 ± 2.8 mm); no patient demonstrated asymmetric septal hypertrophy. All patients had documented spade-shaped deformity of the left ventricle with a ratio of apical thickness to middle anterior free wall thickness >1.3; none had apparent coronary artery disease. The left ventricular end-diastolic pressure averaged 13.9 ± 4.7 mm Hg. A pressure gradient within the left ventricle was not observed in any patient.

ECG follow-up study (Table 2). The follow-up ECG examinations were performed for 5 to 9 years (mean 7.3 ± 1.5) after the initial evaluation in 16 patients (intermediate follow-up group) and after ≥10 years (mean 13.6 ± 2.2) in 21 patients (long-term follow-up group). Eight patients underwent both intermediate and long-term follow-up examinations.

In the intermediate follow-up group, an increase in R wave amplitude ≥5 mm in lead V_5 was noted in four patients and an increase in T wave negativity ≥5 mm in lead V_4 or V_5 in four patients. In contrast, there were decreases (≥5 mm) in R wave amplitude in lead V_5 in four patients and in T wave negativity

Table 2. Electrocardiographic Changes at the Intermediate (5 to 9 years) and the Long-Term (≥10 years) Follow-Up Examinations

	Intermediate		Long Term	
	Initial	Recent	Initial	Recent
Patients	16		21	
Follow-up (yr)	7.3 ± 1.5		13.6 ± 2.2	
Atrial fibrillation	0	1	1	3
R wave in lead V_5 (mm)	42.6 ± 11.6	42.0 ± 14.0	40.7 ± 9.6	26.1 ± 13.8*
High (≥26 mm)	16	15	21	13
Low (≤15 mm)	0	0	0	6
Abnormal Q wave	0	0	0	2
T wave in lead V_4 or V_5 (mm)	−15.1 ± 3.1	−13.7 ± 5.3	−16.5 ± 5.1	−6.9 ± 4.2†
Giant negative T (≤−10 mm)	16	11	21	6
VT on Holter ECG monitoring	0/7	1/4	1/1	6/11

*$p < 0.001$, †$p < 0.01$ compared with value on the initial examination. Data are presented as number of patients or mean value ± SD. ECG = electrocardiographic; VT = ventricular tachycardia of ≥3 consecutive extrasystoles.

in five patients, with a loss of giant negative T waves in all five. However, the average amplitude of the R wave in lead V_5 and T wave negativity in lead V_4 or V_5 did not change significantly in the intermediate follow-up group.

The long-term follow-up examinations revealed remarkable ECG changes. The R wave amplitude in lead V_5 decreased by ≥5 mm in 17 patients, and increased by ≥5 mm in 1 patient, with average amplitude decreasing from 40.7 ± 9.6 to 26.1 ± 13.8 mm. In six patients R wave amplitude decreased to <15 mm and abnormal Q waves developed in two of these. T wave negativity was reduced by ≥5 mm in 17 patients, and was not increased by ≥5 mm in any patient. The average amplitude of negative T waves in lead V_4 or V_5 decreased from −16.5 ± 5.1 to −6.9 ± 4.2 mm. Giant negative T-waves were lost in 15 (71%) of 21 patients who were followed up for ≥10 years. Figure 1 shows tracings from a representative patient with loss of ECG left ventricular hypertrophy and giant negative T waves associated with ventricular tachycardia. The tracings in Figure 2, from another patient, show development of abnormal Q waves in association with regional wall motion abnormalities and fixed thallium perfusion defects in the lateral to apical walls. The repeated coronary angiograms in this patient showed no evidence of epicardial coronary artery disease.

In Figure 3, serial changes in T wave negativity in lead V_4 or V_5 during the initial and follow-up examinations were compared with changes in R wave amplitude in lead V_5. The decreases in T wave negativity closely correlated with decreases in R wave amplitude in lead V_5 ($r = 0.779$, $p < 0.001$). Although ambulatory Holter ECG monitoring was not performed in the majority of patients at the initial evaluation, 6 (55%) of 11 patients in the long-term follow-up group manifested ventricular tachycardia of ≥3 consecutive ventricular extrasystoles.

Echocardiographic follow-up (Table 3). *In the intermediate follow-up group,* one patient developed asymmetric septal hypertrophy over a 9-year period (Fig. 4). However, average thickness of the interventricular septum and left ventricular posterior wall did not show significant changes. There were no significant changes in left ventricular diastolic and systolic diameter or fractional shortening.

In the long-term follow-up group, the average ventricular septal thickness and posterior wall thickness remained unchanged, but asymmetric septal hypertrophy developed over a

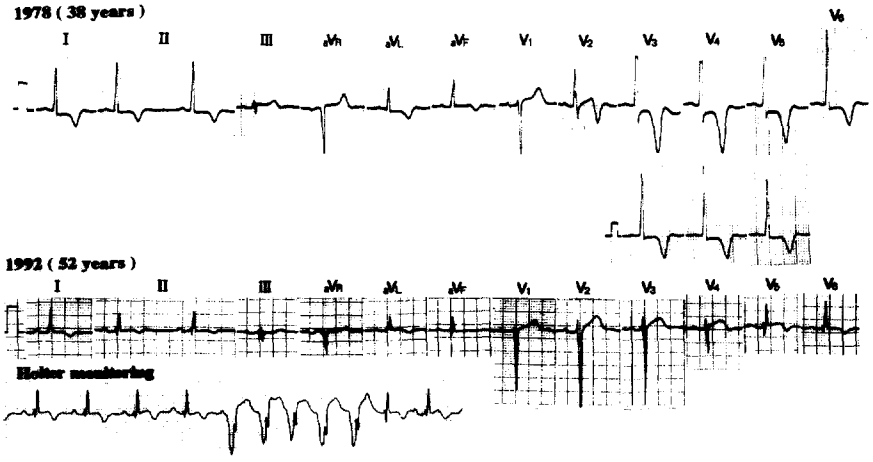


Figure 1. Tracings from a patient with apical hypertrophy show loss of left precordial tall R waves and giant negative T waves over a 14-year follow-up period. Giant negative T waves (−17 mm in lead V_4) and high R waves (50 mm in lead V_5) observed at age 38 years **(top tracing)** had completely disappeared at age 52 **(bottom tracing)**. In the follow-up echocardiograms, thickness of the ventricular septum and posterior wall slightly increased (from 10 to 13 mm and from 9 to 12 mm, respectively), whereas systolic left ventricular function remained within normal limits. Ventricular tachycardia of 5 consecutive extrasystoles was revealed in the follow-up Holter recording.

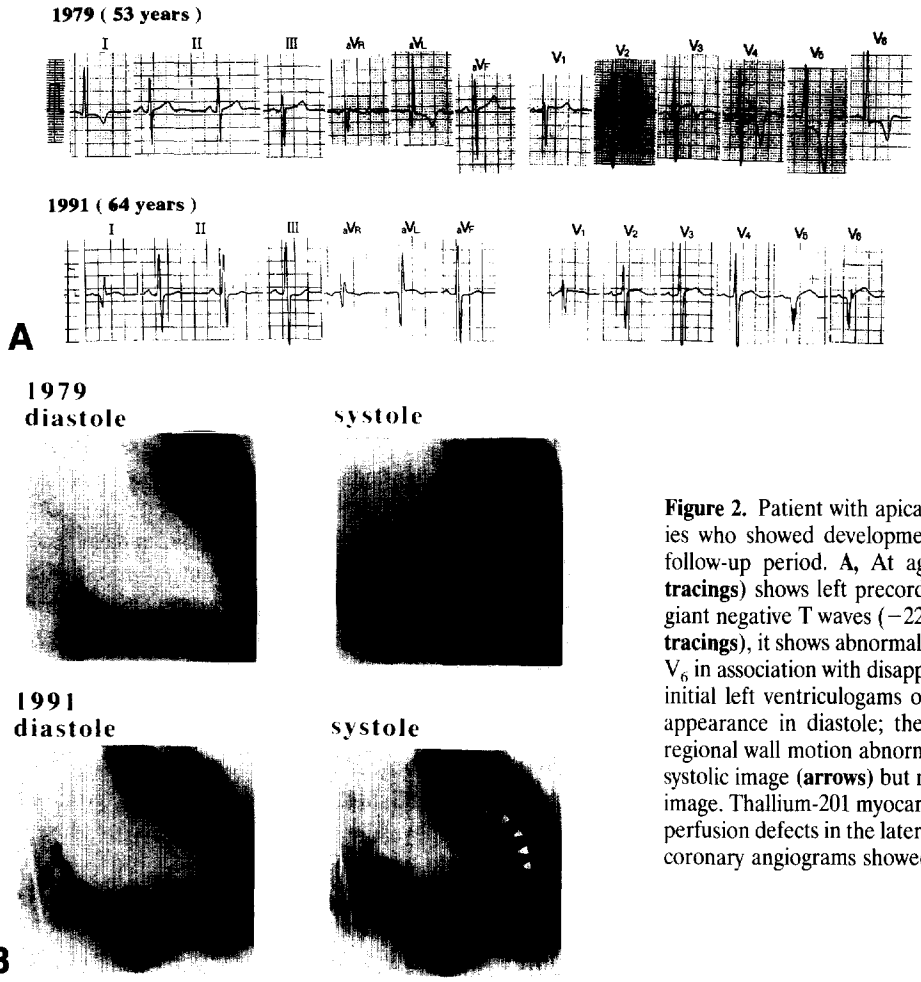
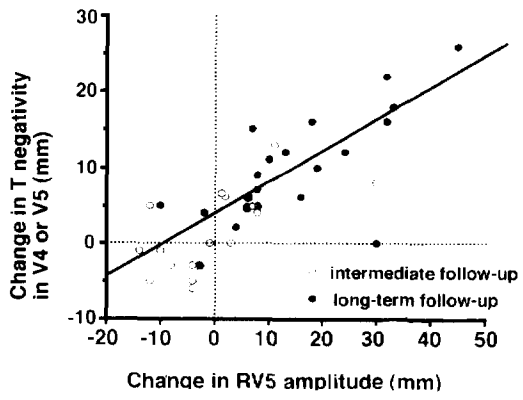


Figure 2. Patient with apical hypertrophy and normal coronary arteries who showed development of abnormal Q waves over a 12-year follow-up period. **A,** At age 53 years, the electrocardiogram **(top tracings)** shows left precordial tall R waves (38 mm in lead V_5) and giant negative T waves (−22 mm in lead V_5). At age 64 years **(bottom tracings)**, it shows abnormal Q waves developing in leads aVL, V_5 and V_6 in association with disappearance of giant negative T waves. **B,** The initial left ventriculogams of this patient **(top)** show a spade-shaped appearance in diastole; the follow-up study **(bottom)** demonstrates regional wall motion abnormalities in the lateral to apical walls in the systolic image **(arrows)** but no spade-shaped deformity in the diastolic image. Thallium-201 myocardial imaging at age 64 years revealed fixed perfusion defects in the lateral to apical walls. The initial and follow-up coronary angiograms showed no evidence of coronary artery disease.

15-year period in one patient (different from the patient in the intermediate group). There were slight but significant increases in left ventricular diameter, whereas fractional shortening remained unchanged. Although one patient whose ECG showed development of Q waves had regional wall motion abnormalities in the left ventriculogram, the follow-up echocardiograms did not show development of left ventricular dilation with reduced fractional shortening resembling dilated cardiomyopathy in any patient.

Figure 3. Graph showing the relation between serial changes in R wave amplitude in lead V_5 (RV5) and T wave negativity in lead V_4 or V_5 in the intermediate **(open circles)** and long-term **(closed circles)** follow-up groups. Decreases in giant T wave negativity closely correlate with reductions in left precordial R waves in lead V_5 ($r = 0.779$, $p < 0.001$).



Discussion

The present study shows a remarkable evolution over a long-term period in the ECG findings of patients with apical hypertrophy of the Japanese form. The characteristic hallmark of this condition, giant negative T waves, disappeared in 71% of patients who were followed up for ≥10 years. Left precordial R waves also substantially decreased in amplitude and abnormal Q waves, implying progressive deterioration of myocardial disease, developed in two patients.

Disappearance of giant negative T waves. These remarkable ECG changes during long-term follow-up have been documented in several case reports (3,5,11,22,23). However, no systematic studies have been previously performed and it is not clear whether the loss of giant negative T waves represents the natural history of apical hypertrophy. Sakamoto et al. (5) followed up 31 patients with apical hypertrophy for 2 to 13

Table 3. Echocardiographic Changes at Intermediate and Long-Term Follow-Up

	Intermediate (n = 16)		Long-Term (n = 21)	
	Initial	Recent	Initial	Recent
Ventricular septal thickness (mm)	13.3 ± 3.2	14.9 ± 5.6	14.5 ± 3.3	16.1 ± 4.8
Posterior wall thickness (mm)	13.0 ± 2.7	13.4 ± 3.1	14.5 ± 2.8	14.1 ± 3.3
Asymmetric septal hypertrophy	0	1	0	1
Left ventricular diameter (mm)				
Diastole	45.3 ± 4.8	46.3 ± 5.4	46.6 ± 5.0	49.2 ± 4.9*
Systole	26.8 ± 4.3	27.8 ± 3.6	27.9 ± 4.9	30.5 ± 4.4*
Fractional shortening (%)	40.8 ± 7.6	40.1 ± 4.4	40.1 ± 8.4	38.3 ± 5.1

*$p < 0.05$ compared with value in the initial examination in the long-term follow-up group. Data are presented as number of patients or mean value ± SD.

years. They reported loss of giant negative T waves associated with decreases in the left precordial R waves over an 11-year period in two patients, but two thirds of their patients showed no appreciable ECG changes. In contrast, the 21 patients in our long-term study group had decreased T wave negativity (from 16.5 ± 5.1 to 6.9 ± 4.2 mm), and giant negative T waves disappeared in 71%. These observations clearly indicate that disappearance of giant negative T waves should be regarded as part of the natural history of this condition. That these dramatic ECG changes were not evident in the intermediate follow-up group may explain why these evolutional changes were not recognized until recently.

The R wave amplitude in lead V_5 decreased substantially in the long-term follow-up group, although it remained unchanged in the intermediate follow-up group. There was a significant correlation between decreases in R wave amplitude and decreases in T wave negativity, indicating a close correlation of giant negative T waves with increased left precordial R waves. However, it is not uncommon to see patients with this condition who had nearly normal findings on previous ECGs taken several years before the diagnosis (1,3,4,11). In our intermediate follow-up group, R wave amplitude progressed ≥5 mm in four patients and T wave negativity increased by ≥5 mm in four patients; in contrast, in the long-term follow-up group, R wave amplitude in lead V_5 increased by >5 mm in only one patient. It is therefore quite likely that the left precordial R waves and negative T waves progress in the initial developmental stage of this condition, reaching their maximal amplitude at approximately the time of diagnosis, and undergo further evolutional changes resulting in disappearances of the characteristic giant negative T waves and tall R waves. These ECG hallmarks of apical hypertrophy now appear to be clinical features that evolve progressively during the natural course of the disease.

Possible mechanisms for ECG changes. Although the mechanism by which giant negative T waves are produced remains speculative, reversal of the sequence of depolarization secondary to severe and localized hypertrophy of the left ventricular apex has been proposed (1,11,12,24–26). In the present long-term follow-up group, R wave amplitude in lead V_5 decreased by an average of 14.6 mm, associated with disappearance of giant negative T waves. R wave amplitude in lead V_5 was reduced to <15 mm in six patients, and Q waves developed in two (Fig. 2). Several case reports have described patients with apical hypertrophy who showed development of left ventricular dilation (22), apical aneurysm (11) or abnormal Q waves (5). It seems likely, therefore, that progression of myocardial disease in the left ventricular apex could be a mechanism for disappearance of giant negative T waves. However, it was difficult to precisely determine the morphology of the left ventricular apex from the two-dimensional echocardiograms, and most patients did not undergo follow-up left ventriculography. The precise mechanisms for these ECG changes remain to be further elucidated.

Clinical implications. The benign course of the Japanese form of apical hypertrophy has been generally accepted (5,11,13,27). No cardiac death was reported in the present patients with apical hypertrophy, including those who did not have the follow-up examinations. However, 55% of the long-term follow-up group demonstrated ventricular tachycardia on Holter ECG monitoring. Therefore, we should now recognize that sudden death due to ventricular arrhythmias may occur in patients with apical hypertrophy of the Japanese form.

Considerable controversy and confusion persist regarding the definition and diagnosis of apical hypertrophy (5,11,13,14). For this study we therefore selected patients with the "pure" Japanese form of apical hypertrophy who had three hallmarks of the condition: left precordial giant negative T waves, tall R waves and spade-shaped configuration of the left ventricle. We excluded patients who showed asymmetric septal hypertrophy in the two-dimensional echocardiograms. Our study patients thus demonstrated the typical clinical profie of the Japanese form: predominance of older men, rare genetic background, frequent prior history of hypertension and minimal to mild symptoms. In contrast, studies of non-Japanese patients with apical hypertrophy (western form) have described infrequent presentation of giant negative T waves but later development of marked symptoms. In such patients, genetic transmission was often observed (6–15), with first-degree relatives demonstrating the typical asymmetric septal hypertrophy. Nevertheless, asymmetric septal hypertrophy developed over a 9- and 15-year follow-up period in two of our patients. This observa-

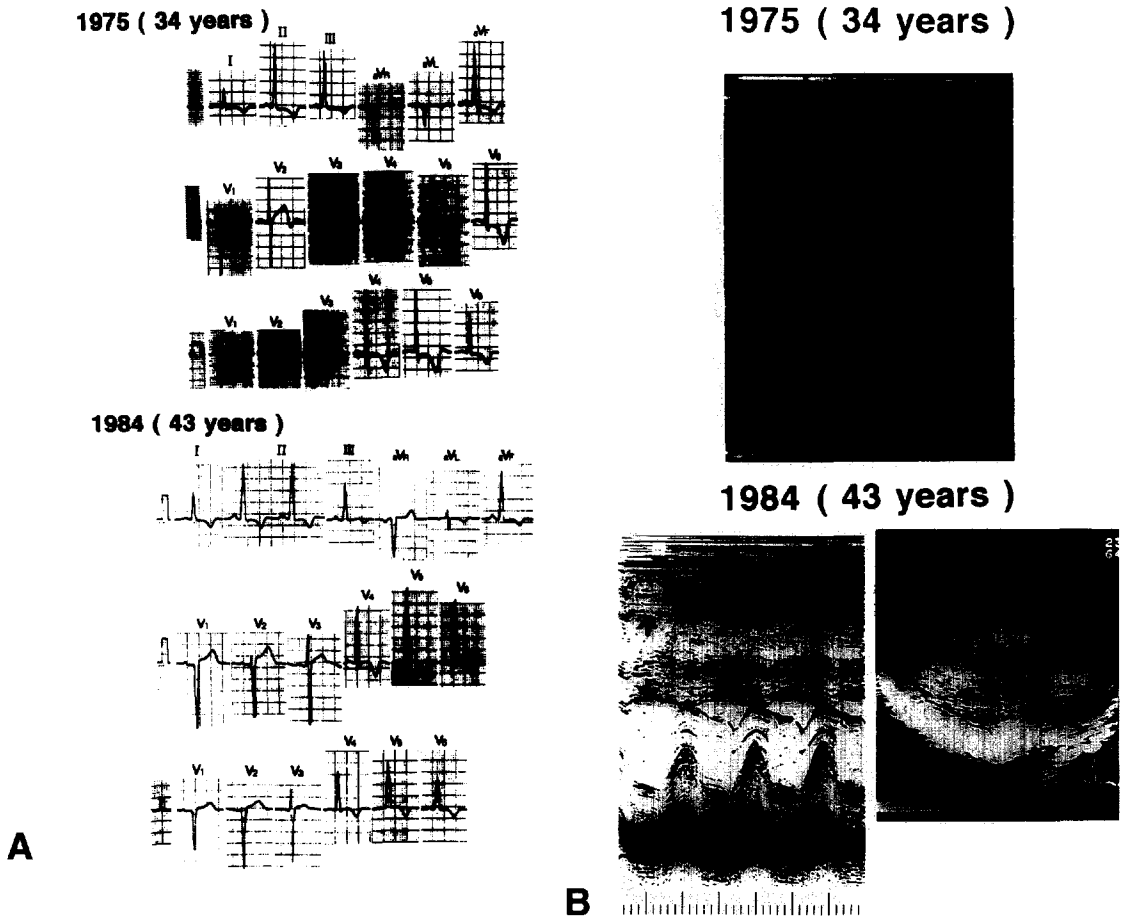


Figure 4. Electrocardiograms (ECGs) **(A)** and echocardiograms **(B)** from a patient with initial apical hypertrophy who showed development of asymmetric septal hypertrophy over a 9-year period. The ECG tracings in 1975 **(A, top)**, at age 34 years, show tall R waves (52 mm in lead V_5) and giant negative T waves (−17 mm in lead V_5), whereas the 1975 M-mode study **(B, top)** shows symmetric septal and posterior wall thickening (15 and 16 mm, respectively). The 1984 ECG **(A, bottom)**, at age 43 years, shows decreases in R wave amplitude and T wave negativity. The 1984 two-dimensional echocardiogram **(B, bottom right)** shows asymmetric septal hypertrophy (32 mm), although the right ventricular side of the ventricular septum was not clearly delineated in the M-mode study **(bottom left)**. **Arrows** indicate the right and left ventricular sides of the ventricular septum.

tion indicates that apical hypertrophy might be an initial manifestation of ventricular hypertrophy that later progresses to typical asymmetric septal hypertrophy. However, we believe that this morphologic transition from apical to septal hypertrophy is uncommon when patients with the typical Japanese form of apical hypertrophy are selected.

Although there were slight but significant increases in left ventricular diameter in our long-term follow-up group, left ventricular dilation and systolic dysfunction resembling dilated cardiomyopathy did not develop in any patient. However, the striking ECG changes in some of these patients suggest a slow but progressive nature of the cardiomyopathic disease process of this condition that requires further careful follow-up studies.

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